Seizure Pathology

Introduction

Neurons depolarize. Axons carry that depolarization to the next neurons they synapse onto. Tract axons don't RUN in fascicles; they ARE in fascicles. The axons are present all the time. What moves is the depolarization, the action potential along each axon. These depolarizations are not typically coordinated—the axon of one neuron doesn't communicate with the axon of the neuron next to it in order to depolarize an action potential. Each axon is myelinated and separated from the others by oligodendrocytes. That means the axons of a given fascicle will depolarize at different times, and thus depolarization is **asynchronous**. Most of the nervous system is set up to have multiple inputs and one output (the axon). Individual cells, individual cell bodies and axons, depolarize when they are supposed to, not when the rest of the fascicle or tract depolarizes. This cell-by-cell regulation enables near-infinite combinations of different synapses firing across the brain. It isn't infinite, of course, but to put it into perspective, there are an estimated 1.4×10^{14} synapses in the cortex (just the cortex, not the brain). At any given time, each synapse could be firing or not firing, in nearly any permutation. Then consider these permutations over time, changing every millisecond. The brain functions because there are independent axons, independent synapses, that are not working together. If they were **synchronous**, the brain would be dysfunctional.

A **seizure** is caused by the **hypersynchronization of neural networks** in the cerebral cortex. When all the neurons fire together, it is really easy to see on an **electroencephalogram** (EEG). The spiking patterns occur because the **brain is in sync**. It should NOT be. Normal function is asynchronous. When neurons sync with each other, they aren't performing normal functions. The affected part of the brain will be dysfunctional. This could be as simple as the motor cortex controlling the right index finger, causing the finger to wiggle, or it could be as catastrophic as the entire cortex, which compromises all functions.

Epilepsy is a diagnosis, a disease that presents with the symptom of seizure. **Seizure** can be caused by epilepsy or have an underlying cause, as we will discuss in the next section. Epilepsy and seizures are related but not the same thing, and so receive different treatments. Epilepsy treatment focuses on preventing the next seizure. Seizure treatment focuses on aborting the seizure and investigating the etiology of the seizure.

This lesson is about seizure, epilepsy, and status epilepticus—severe refractory seizures that are life threatening. The nomenclature for seizure changed in 2017. Gone are simple vs. complex, partial vs. generalized. The concept is the same, but the new version has better words. In the video, only the new way is presented. In this set of notes, we will also present the old way, just in case you need a translator while looking at another resource.

Provoked vs. Unprovoked

A seizure is a symptom either of an acute derangement (provoked) or of chronic epilepsy (unprovoked).

Unprovoked seizures are due to an unknown etiology, a pre-existing brain lesion, or progressive nervous system disorder. The cause of the seizure comes from within the neural networks of the brain parenchyma in an otherwise stable ecosystem. These have a high chance of progressing to epilepsy. Practically, as brain lesions or neuron degeneration can't be reversed at this point in medicine, unprovoked seizures equate with epilepsy.

Provoked seizures (also called "acute symptomatic seizures") are secondary to something else. The mnemonic "VITAMINS" helps identify potentially reversible causes of a seizure. In most of the VITAMINS cases, the risk for future epilepsy is low. Note that VITAMINS includes pre-existing brain

lesions because it was developed before the new definition of unprovoked. We still include it because, although strokes and brain bleeds confer an increased risk of future epilepsy, they are etiologies that must be considered (and often ruled out with brain imaging) in someone presenting with an acute seizure, especially a first-time seizure.

	STANDS FOR	EXAMPLES
V	Vascular	Brain bleed (epidural, subdural, subarachnoid, intraparenchymal), stroke, vasculitis
I	Infection	Meningitis, encephalitis
T	Trauma	TBI, skull fracture, concussion, contusion
A	Autoimmune	Cerebritis of lupus, demyelinating diseases
M	Metabolic	Low oxygen, low glucose, calcium, sodium, water
I	Ingestion/Withdrawal	Benzodiazepine withdrawal, alcohol withdrawal Too many to list for ingestion
N	Neoplasm	Meningioma*, glioblastoma, metastasis
S	pSych	Pseudoseizures, interactions between medications, misdiagnosed seizure as a psychiatric disorder

Table 3.1: Causes of Acute Seizure

A patient with well-controlled epilepsy may still have a seizure. The problem is that not every seizure is an emergency. Seizures that are brief and without injury need not be evaluated. When someone without an epilepsy diagnosis has a seizure, VITAMINS must be investigated. When a patient with diagnosed epilepsy has a seizure, it might just be a breakthrough seizure, it might be that the medication needs to be changed, or it might be because of VITAMINS. At this stage in your training, on any licensing exam, you will be provided a vignette about either [no epilepsy, first-time seizure] or [epilepsy requiring dose titration].

Status epilepticus is a life-threatening emergency of refractory seizures. The old definition of status epilepticus was 20 minutes. It is now **5 minutes**. If a patient has **continuous seizure activity for 5 minutes** or has **two seizures without return to baseline cognition**, it is considered status epilepticus. The old definition was vague and included time while postictal. Some patients may take longer to return to baseline awareness, and those with gradual improvement may need no intervention at all. Patients who have seizure activity for ≥ 5 minutes are cooking their brains—seizures are intensely metabolic. Depolarizations mean lots of Na^+/K^+-ATPase activity to restore the concentration gradient. The brain is suffering during the seizure, and letting it go on for 20 minutes led to worse outcomes.

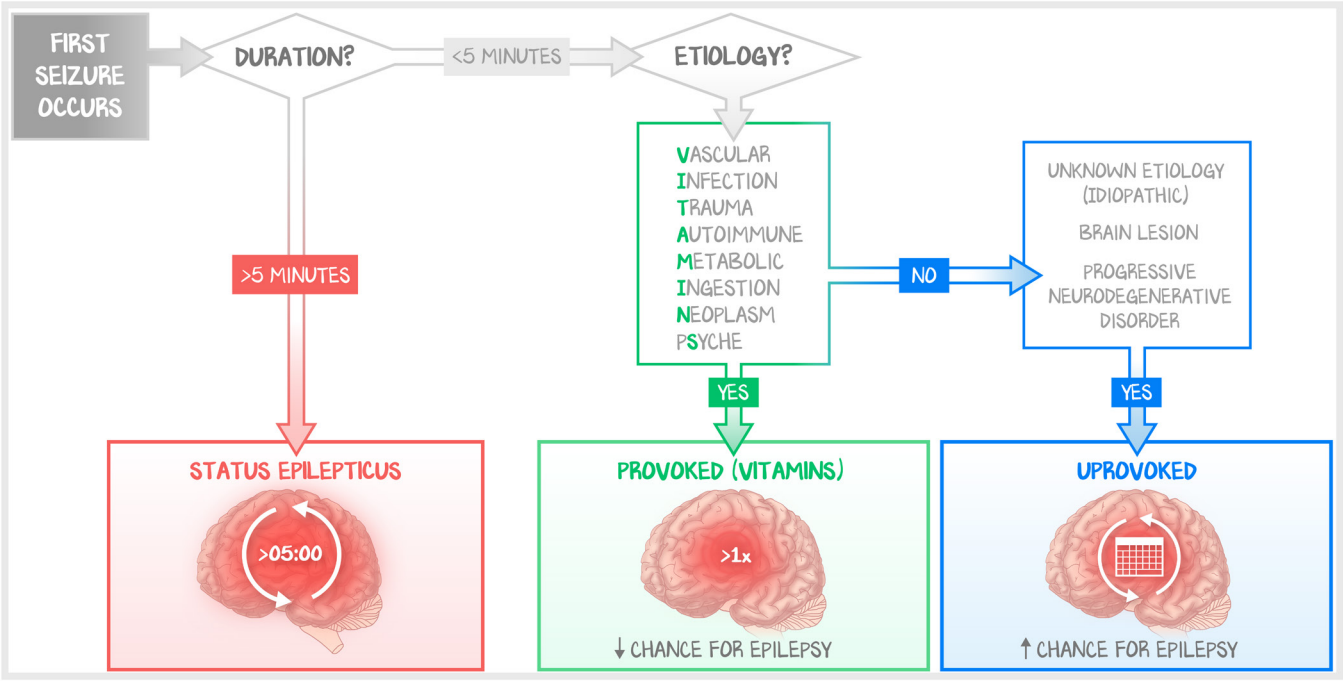

Figure 3.1: Provoked and Unprovoked Seizures and Status Epilepticus
Always consider whether a seizure has occurred or is still occurring—status epilepticus is a life-threatening emergency. But most seizures are not status epilepticus. When someone has their first seizure, consider VITAMINS to rule out a secondary cause of the seizure (called provoked). If provoked, correcting the underlying defect may be enough to prevent future seizures. If unprovoked, then the patient has a higher risk for developing the syndrome characterized by the symptom of seizures, called epilepsy.

The Old Way

Simple vs. complex. Prior to 2017, "simple seizure" meant one with no **loss of consciousness**, and "complex seizure" meant one with loss of consciousness. The problem was that "consciousness," and the loss thereof, is heavily subjective. As described in the next section, awareness and recall of events during the seizure is a much more objective way of naming seizures. "Simple" is now "with awareness," and "complex" is now "without awareness."

Partial vs. generalized. "Partial" has been replaced by "focal." "Generalized" hasn't changed. Many providers interpreted partial seizures as "motor symptoms, not grand mal." Even the term *grand mal seizure* (a generalized tonic-clonic motor seizure) has been removed from the lexicon. Instead, the symptom is added to the seizure name—motor, cognitive, autonomic, etc.

International League Against Epilepsy (ILAE) Framework

What follows are the updates in nomenclature—how to name a seizure. It takes three features into account—onset, awareness, and motor symptoms. The goals are to bring clarity to the characterization of the seizure and best communicate it to others by capturing what happened during that seizure in the diagnosis name. This may be getting a little ahead of the basic sciences, but the goal was not only to bring clarity to providers but also to establish a means of crossing into research, documentation (diagnosis codes), and billing (billing codes). By capturing the characteristics in the seizures' names, a common link now exists between all domains of health care delivery. At the time of this writing (2020), the CDC and Wikipedia still use the 1981 classification of seizures. The new classification does not represent a fundamental change but allows greater flexibility and transparency in naming seizure types.

Onset can be focal or generalized. A **focal-onset** seizure is caused by synchronized discharges that remain **unilateral**, originating in **one hemisphere** of the brain. The circuit can be any size, and in any tissue, thus the symptoms and retention of awareness vary greatly. A **generalized-onset** seizure is any abnormal behavior that is caused by synchronized discharges on **both** sides of the brain. Those discharges are NOT necessarily symmetrical, and they don't need to be discharges of the entire cortex. It's just that, when synchronous discharges occur bilaterally, there is going to be impaired awareness. The words "focal" (formerly "partial") and "generalized" at the beginning of a seizure name are assumed to describe the **onset**. A seizure with focal onset can progress to become generalized (formerly "Jacksonian march"), and is, therefore, named focal-to-generalized. Those are the three seizure types, used to determine treatment (in the next lesson)—focal, focal-to-generalized, and generalized onset.

Awareness was adopted in place of "consciousness." The ILAE defines **retained awareness** as knowledge of one's self and environment. In this context, awareness refers to the perception or knowledge of events occurring **during a seizure**. Waking up without recall of the events but identifying the obvious signs that a seizure has occurred does not count. **Recall** is a surrogate for awareness during the event and only fails in the minuscule fraction of amnesic seizures that erase the memory of the event, despite retained awareness during the event. A generalized seizure always leads to impaired awareness. Focal seizures can have **retained awareness** or **impaired awareness**. Responsiveness does not equate with awareness, as some patients may be aware but are immobilized by the seizure.

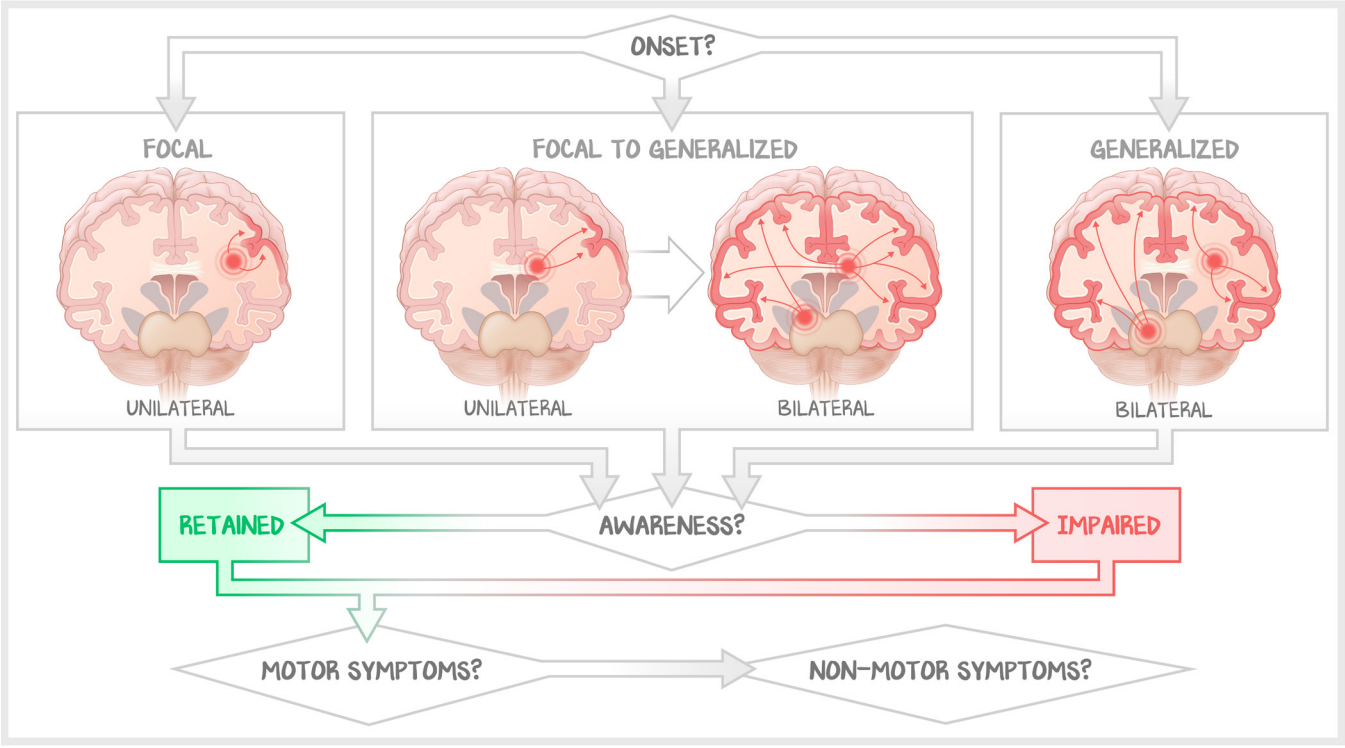

Figure 3.2: Naming Seizures For Dummies
The ILAE recognized that not everyone was going to spend the time to learn the details of naming a seizure, so they kept it easy for those providers who are not seizure specialists. It comes down to onset (focal, focal-to-generalized, generalized), awareness (yes/no), and motor symptoms (yes/no). This way, those who provide medical care can still get close—specifically enabling the identification of the two seizure illness scripts that every provider should know (absence and generalized tonic-clonic). Absence is generalized, impaired awareness, non-motor. "Grand mal" (now excluded from the lexicon) is generalized, impaired awareness, tonic-clonic. Everything else is "other."

The next section shows you the details of how to name a seizure appropriately and demonstrates the complexity of doing it right. The ILAE recognized that not every provider is going to be able (or willing) to be specific, so they provided a simplified version of the **motor** component. For generalized-onset seizures, the simplified version asks you to choose one of three: **nonmotor** (absence), **motor tonic-clonic** (what was referred to as grand mal), or **motor other**. Non-motor and motor tonic-clonic conveniently pairs with the older nomenclature of the two generalized seizure illness scripts we want you to learn—tonic-clonic and absence. It isn't as accurate as doing it right, but this simplicity enables everyone who isn't a seizure specialist to come close to the right answer. For focal-onset seizures, the simplified version asks you to choose between two options—**motor** or **nonmotor—**without further separation.

We are going to show you the right way to do it, then, later in this lesson, tell you the specific illness scripts you need to recognize for licensure.

Subdividing Generalized-Onset Seizures' Motor Component

The right way to name seizures involves knowing the definitions of tonic, clonic, myoclonic, and atonic. Here's the takeaway: **atonic** causes a loss of motor function, **myoclonic** causes an ultra-brief (< 0.1 sec) muscle jerk, **tonic** causes a sustained (20 sec) contraction of any muscle, and **clonic** causes multiple contractions and relaxations of any muscle in a rhythmic pattern, occurring every 2–3 seconds. Definitions available online are circular and confusing. The right answer is available, but you have to know which resource to listen to. Hopefully, you won't have to go elsewhere. The problem is that there is no single "classic" seizure type or presentation. After this discussion of the different motor presentations, we are going to give you two "classic" generalized-onset seizure types. But first, we want you to see that they are NOT classic for people who have epilepsy, so you know that "classic" means "on licensing exams for novice learners."

Myoclonic seizures are usually focal onset, happen once, and cause the patient to spill their coffee, flip their food into the air, or trip while walking—any muscle movement. The patient is usually aware of it, or at least its consequences. Myoclonic seizures are so brief that there isn't time for loss of awareness, and so specific that only a tiny region of the brain is affected. All of this means that myoclonic seizures are usually focal onset. However, when myoclonic seizures are involved in generalized-onset seizures, it is usually the eyelid during an absence seizure or part of a juvenile syndrome of myoclonic-tonic-clonic seizure.

Tonic seizures are a sustained contraction of all muscles for approximately 20 seconds. They usually happen while **asleep**. If they happen while awake, the person will fall. Certain depictions of a tonic seizure involve the extension of the arms, whereas other depictions show flexion, so students attempt to learn that tonic is one direction and clonic the other and are then confused when each is depicted as the other. Back in his paramedic days, Dr. Williams was taught the deCOORSdeicate and decerebrate pneumonic—holding two Coors Lights with both arms flexed was one movement, decerebrate "the other one," both arms extended. It was not malice that these things were taught that way. Any attempt to find examples of a seizure online is met with conflicting and confusing information. This is because illustrations are fixed in time but attempt to depict the progression of a tonic-clonic seizure over time (see our illustration, then #TeamAng below). A purely **tonic seizure** is a **sustained contraction of muscles**. It doesn't matter whether they are flexed or extended. The **arching of the back** is a common feature of many tonic seizures, but there is no stereotypical contraction—a tonic seizure involves sustained contraction of any muscle(s), flexion or extension. When you see Angelique move into a tonic phase of her seizure (end of this lesson), you will realize how heterogeneous the contractions are.

Clonic seizures are a repetitive, rhythmic contraction and relaxation of muscle groups. This is what gave rise to the term **convulsion** (which has been removed from the epilepsy lexicon). Patients who fake seizures tend to move their muscles around wildly, emulating the "seizures" they have seen on

TV and in movies, unaware that depictions of seizure by actors who are not having a seizure look very different from actual seizures. Unless you know someone with epilepsy or have witnessed a patient's tonic-clonic seizure firsthand, you probably also have the visual from TV and movies in mind. We did, too, and the prevalence of these inaccurate media depictions is one of the reasons the ILAE changed the nomenclature. Like in tonic seizure, it **does not matter which muscle groups** are involved, only that there is a **rhythmic**, **repetitive** contraction and relaxation of the same muscle group.

For both tonic and clonic generalized seizures, **contraction can be asymmetric**.

Atonic seizure means a loss of motor function. There is a sudden loss of muscle control. This is colloquially known as a "drop seizure" because, even when focal and aware, the loss of motor control results in the patient falling.

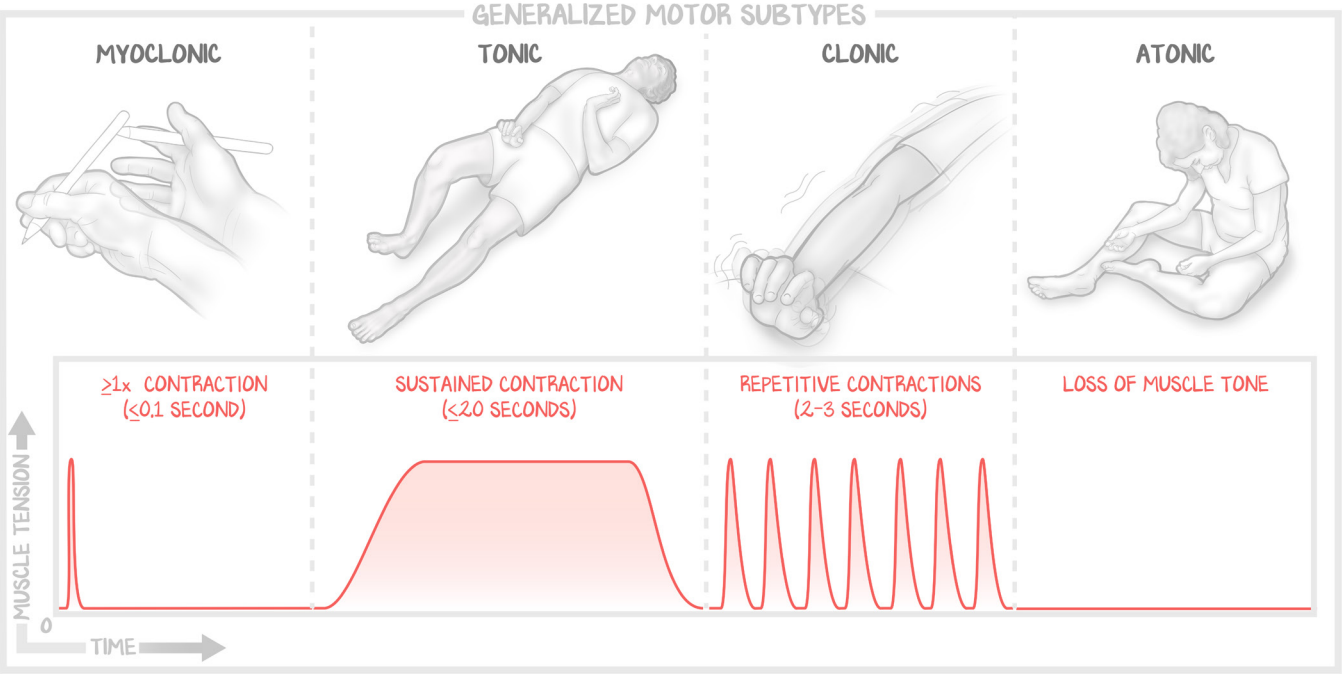

Figure 3.3: Generalized Motor Subtypes
The goal here is for you to recognize what a seizure looks like over time. Angelique's video (link at the end of this lesson) will serve you infinitely more than this illustration. But we want you to see something similar to the entirely misleading information you'll find littering the subject of epilepsy. Myoclonic is an ultra-short jerk, a brief contraction and relaxation of a muscle. Tonic contractions are flexion or extension—any muscle or all of them—and sustained over time. Clonic seizures are why "convulsions" (excluded from the current lexicon) were used to describe seizure behavior. Clonic seizures involve the repeated contraction and relaxation of muscle groups, cycling on a 2–3-second cycle (the video says 2–5, sources vary). Atonic seizures are a loss of tone.

Generalized-Onset Seizure Illness Scripts That You Should Recognize

Despite what we just told you as truth, these are the two well-defined illness scripts you should be aware of.

Tonic-clonic seizures (formerly grand mal seizures) are likely the seizure you imagine when you see the word seizure. There is a **tonic phase**, during which tongue-biting can occur (protrusion of the tongue and clamping of the jaw are both contractions), the back arches, and the patient remains contracted for up to 20 seconds. The tonic phase ends. The **clonic phase** is when the "convulsions" (a term no longer used in epilepsy) occur: the rhythmic contraction and relaxation of muscle every 2–3 seconds. There is no set duration. The patient can go back into the tonic phase, back into the clonic phase, or simply not move. This is a generalized-onset seizure, so there is a loss of consciousness, now termed **lack of awareness** of the seizure (and therefore, the patient will **not remember** the seizure). When the seizure is over, there will be a **postictal state**. They will take several minutes to regain full awareness. The change is gradual, and noticeable changes will occur. There will be no more tonic or clonic contractions. The patient will start to move their extremities, look around, and eventually talk. To an observer, coming out of a postictal state looks something like someone being woken up from a deep sleep. Not a startled response, but a gradual awakening and eventual realization of where they are and what might have just happened (if they know they have epilepsy, they will realize). Some seizures are preceded by an **aura**—any neurologic symptom—that heralds the arrival of the seizure.

Absence seizures involve the retention of motor function, but **complete loss of awareness**. They are typically seen in children aged 4–8. Their **duration is short** (5–15 seconds), and they occur in clusters, up to **100 seizures per day**. There may be **automatisms** (lip-smacking, blinking, fiddling with a button), but there is certainly an **absent stare**. The EEG will demonstrate 3-Hz **spike and wave** discharges (they occur three times in one second). To the child, the world is a clustered mess. The teacher will be on A, talking about an apple, and suddenly she's at D, talking about dinosaurs. Then as soon as she starts E, she finishes it by talking about a giraffe. Then the next thing the child knows, the teacher is in his face asking if he's been paying attention and demanding he stop smacking his lips like that. To him, he *has* been paying attention and hasn't been smacking his lips, unaware of the interruptions in awareness. We used "he" on purpose. This is often tested against ADHD, which is more commonly diagnosed in boys. Always consider absence seizure in a child being tested for ADHD. The child with ADHD is easily distractible, doesn't pay attention, and is interruptive. The behavior happens at school and home. Absence seizures involve the inability to follow along (patients appear easily distracted) and happen everywhere all the time.

Subdividing Focal-Onset Seizures' "Motor" Component—Symptom Component

Do not attempt to memorize this table. We are demonstrating that **seizures can happen anywhere in the cortex**, and the region of the cortex that a seizure affects will determine the symptoms. Unlike generalized-onset seizures, focal-onset seizures don't have a classic set of presentations. And like generalized-onset seizures, focal-onset seizures are divided into **motor** and **nonmotor**. The problem is that, for focal-onset seizures, nonmotor can mean literally any other symptoms, which have their own categories with specific symptoms added to each—cognitive, automatisms, autonomic, emotional, or sensory.

COGNITIVE	AUTOMATISMS	AUTONOMIC
Acalculia	Aggression	Asystole
Aphasia	Eye-blinking	Bradycardia
Attention impairment	Head-nodding	Erection
Déjà vu or jamais vu	Manual	Flushing
Dissociation	Oral-facial	Gastrointestinal
Dysphasia	Pedaling	Hyper/hypoventilation
Hallucinations	Pelvic thrusting	Nausea or vomiting
Illusions	Perseveration	Pallor
Memory impairment	Running (cursive)	Palpitations
Neglect	Sexual	Piloerection
Forced thinking	Undressing	Respiratory changes
Responsiveness impairment	Vocalization/speech	Tachycardia
	Walking	
EMOTIONAL OR AFFECTIVE	**MOTOR**	**SENSORY**
Agitation	Dysarthria	Auditory
Anger	Dystonic	Gustatory
Anxiety	Fencer's posture (figure-of-4)	Hot-cold sensations
Crying (dacrystic)	Incoordination	Olfactory
Fear	Jacksonian	Somatosensory
Laughing (gelastic)	Paralysis	Vestibular
Paranoia	Paresis	Visual
Pleasure	Versive	

Table 3.2: All of the Possible Classifications of Focal Seizures

In a presentation at Tulane (where Dr. Williams went to medical school and did his Internal Medicine residency training), a neurologist described a case of psychotic disorder. A patient was hallucinating, seeing spiders crawling all over her floor. She was hospitalized and placed on antipsychotics, without effect. Antipsychotics lower the seizure threshold, making it easier for a seizure to start. After 2 weeks of amplifying the antipsychotics and needing sedation to calm her (because her "psychosis" was worsening despite medications), the neurologist presenting the case was consulted. When that patient was seeing spiders crawling on the floor and reacting to them, it was not a psychotic hallucination. It was her seizure, shown on EEG. The antipsychotics made the seizures worse. The benzodiazepines she was given for sedation had been aborting her seizure, not abating psychosis. This is an extreme story that doesn't happen often, but it was so poignant that everyone paid attention to both the presenter and the message—a person's seizures can present with any symptom, not just the tonic-clonic seizures popularized by TV and movies.

Unknown

Especially for unwitnessed first-time seizures, the etiology of a seizure may not be known. The ILAE wanted there to be a placeholder term for if there were no patient awareness or good statements gathered from bystanders, one that would eventually be filled in by a repeat seizure or a diagnosis by EEG. So, at times, there may be an Unknown Seizure. You won't see this.

Epilepsy Types

A seizure is a hypersynchronous firing of the brain. It is a symptom. Epilepsy is a diagnosis, a condition that warrants treatment with antiepileptic drugs (AEDs). Epilepsy is defined by having **two or more unprovoked seizures** or having any known **epilepsy syndrome** (Lennox-Gastaut syndrome, benign rolandic epilepsy, and things we don't want you to learn).

Epilepsy is classified the same way seizures are classified—focal, generalized, focal-to-generalized. The **type of epilepsy is defined by the EEG pattern**, determined by **where the seizure originated**. The EEG identifies neural circuits. If these neural circuits are detected on only one hemisphere, it is **focal epilepsy**. If there are bilateral circuits at onset, it is **generalized epilepsy**. If the circuits start unilaterally and rapidly become bilateral, that counts as generalized. If the circuit begins unilaterally and gradually becomes bilateral, that is **focused-to-generalized epilepsy**.

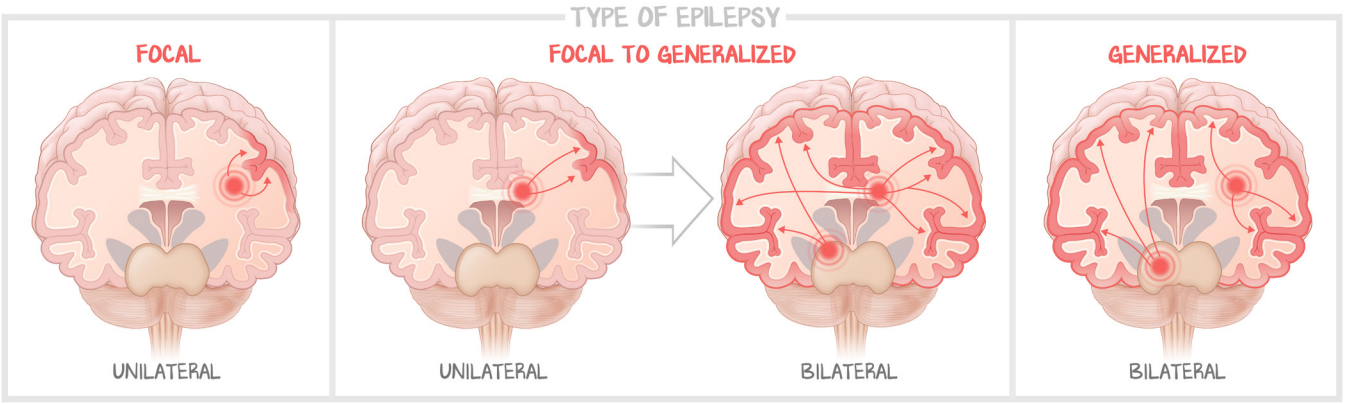

Figure 3.4: Epilepsy—Where The Seizure Starts
You should name seizures based on their onset—focal, focal-to-generalized, generalized. When diagnosed with epilepsy by EEG, a similar construct is used. People with epilepsy do not always have the same seizure. But knowing whether they have focal seizures versus generalized helps define which antiepileptic drug is best for them.

Experiencing a Seizure

#TeamAng. We are in no way affiliated with TeamAng. We found her YouTube channel while trying to find examples of real patients with epilepsy having real seizures. For an organization, institution, school, hospital, or anyone to ask a person to do what Angelique does would be strictly unethical, immoral, and borderline illegal. We don't know why she does it. We believe that she should be on anti-seizure medications. She should not seize. We do not condone refusing treatment for a controllable disease, and we don't know whether she is receiving treatment. But we also believe that humans have a choice. And if this woman chooses to seize, record her seizures, and post them for the world to see, then we feel it is even more unethical and immoral not to use her videos to educate those who are training to be masters of health and disease—you. This message is not meant for people who have epilepsy or have a loved one who does. You know what seizures look like. This message is for everyone else who doesn't. And that one time you saw someone maybe seize across the street doesn't count.

This one video (link below) demonstrates elements of a generalized tonic-clonic seizure so vividly, and we highly suggest you watch it. Her YouTube channel catalogs her seizures so well, and the spectrum of the seizures she has is so vast. Whatever her motivation, the effect of her videos is to spread awareness about living with epilepsy and what seizures look like.

We want to be ultra-clear. Angelique should not suffer as she does. Her sacrifice is not condoned. But her sacrifice is respected and appreciated. This is definitely, a thousand percent, NOT a criticism of Angelique's choices. We want you to learn that if someone has a disease that is controllable with medications, you should treat the disease. We also want you to learn that humans can do as they please, and your patient may reject your recommendations.

We contacted her to ask if we could share her video with you. Her answer was an emphatic yes. Appreciate her experience, feel sorrow for her pain, witness what most providers have never actually seen, feel rage for her lack of care, weep for her mother's suffering (and honesty), and know that any difficulty you have watching this video (which you should watch at normal speed) will ultimately be translated to empathy and understanding.

https://www.youtube.com/watch?v=UWmFMSQeCBM—If you watch only one of her videos, watch this one. We'll include timestamps in the text when something is obvious. There are many subtleties, but we want you to focus on the obvious elements (the science) while you also experience the emotion of her experience. The video begins as Ang senses an aura. She has a focal seizure with unknown symptoms. She is aware until minute 1:45 (the camera changes to her mom's phone). She has automatisms at 3:15, which turns into a clonic seizure at 3:25. The rapid breathing is probably another clonic seizure or a continuation of the one that started at 3:25. She starts having a tonic seizure at 4:45. The tonic seizure lasts almost a minute, her mother's cell phone camera capturing the tonic contractions. At 5:50, an obvious clonic seizure starts. At 6:19, the seizure ends. She is postictal and gradually regains awareness. First, blinking in response to her mother, then actively looking around when her mother returns to the car. At minute 10:00, she speaks in response to a question but is disoriented to her surroundings. Her seizure lasted more than 5 minutes. She took nearly 30 minutes to return to baseline. Both define status epilepticus.

https://www.youtube.com/watch?v=zPNVYFRhthg—this is an enactment by the Epilepsy Society in the UK. The drama is so fake, but it shows what a myoclonic seizure is. The spoon flipping the cereal is a seizure, a seizure she had because she didn't sleep. Compare that to Ang's clonic seizure at 5:50, and you will not confuse the two.